Clinical Center Pharmacy Department

Pharmacy Update

March/April 1997

In This Issue

Drug Information Service
Pharmacy Department
Warren G. Magnuson Clinical Center
National Institutes of Health
Bethesda, Maryland 20892-1196

Charles E. Daniels, Ph.D.
Chief, Pharmacy Department

Editor-in-Chief
Karim Anton Calis, Pharm.D., M.P.H.
Coordinator, Drug Information Service, and Endocrinology Clinical Pharmacy Specialist
kcalis@nih.gov

Associate Editor
Iris P. Masucci, Pharm.D.
Specialized Resident in Drug Information Practice and Pharmacotherapy

Cyclosporine for Microemulsion (Neoral®)

Cyclosporine (Sandimmune®) is an immunosuppressive agent that is widely used in solid organ and bone marrow transplants as well as in a variety of autoimmune disorders. The oral form of Sandimmune® has incomplete and variable absorption making it difficult to achieve a stable oral dosing regimen. Neoral® (cyclosporine for microemulsion) is a new formulation of cyclosporine that was approved in 1995. It was developed to improve the drug's absorption characteristics after oral administration.

Description: Neoral® (cyclosporine for microemulsion) is an oral formulation of cyclosporine that immediately forms a microemulsion in an aqueous environment. It is manufactured by Novartis Pharmaceuticals (formerly Sandoz Pharmaceuticals), and is available as 25 mg and 100 mg soft gelatin capsules, and as a 100 mg/mL oral solution.

Indications: Cyclosporine (both formulations) is indicated for the prophylaxis of organ rejection in kidney, liver, and heart allogeneic transplants. Cyclosporine has been used in combination with azathiaprine and corticosteroids.

Pharmacology: Cyclosporine is a potent immunosuppressive agent. It has been demonstrated to suppress some humoral immunity and to a greater extent, cell-medicated immune reactions such as allograft rejection, delayed hypersensitivity, experimental allergic encephalomyelitis, Freund's adjuvant arthritis, and graft vs. host disease in many animal species for a variety of organs. Cyclosporine produces specific and reversible inhibition of immunocompetent lymphocytes in the G0- and G1-phases of the cell cycle.

T-lymphocytes are preferentially inhibited. The T-helper cell is the main target, although the T-suppressor cell may also be suppressed. Cyclosporine also inhibits lymphokine production and release, including interleukin-2.[1]

Pharmacokinetics: After oral administration of the standard formulation of cyclosporine (Sandimmune®), an oil-in-water droplet mixture is formed on

contact with gastrointestinal þuids. EmulsiÞcation of this mixture by bile salts is required before digestion of the oily droplets and release of cyclosporine. This emulsiÞcation step is what makes the absorption of cyclosporine dependent on bile þow, food intake, and gastrointestinal motility, and therefore unpredictable. On contact with gastrointestinal þuids, Neoral® forms a homogenous, monophasic microemulsion which mimics the mixed micellar phase of cyclosporine absorption seen with the standard formulation.[2]

Neoral® is more rapidly and consistently absorbed than Sandimmune® and its relative bioavailability is larger. As a result, trough cyclosporine blood concentrations can be more closely related to total drug exposure during a dosage interval than with Sandimmune®. The pharmacokinetic parameters of Neoral® are less affected by food than those of Sandimmune®.[3]

Cyclosporine is distributed in the plasma, erythrocytes, lymphocytes, and granulocytes. In the plasma, cyclosporine is approximately 90% bound to proteins. Cyclosporine is metabolized by the cytochrome P450 III-A enzyme system in the liver and, to a lesser degree, in the gastrointestinal tract and the kidney. It is metabolized to at least 25 metabolites. Neoral® has a half-life of 8.4 hours, with a range of 5 to 18 hours. Excretion is primarily biliary with only 6% of the dose excreted unchanged in the urine. Renal failure or dialysis do not signiÞcantly alter cyclosporine clearance.[1]

Neoral®, when compared with Sandimmune®, has increased bioavailability, decreased intra- and inter-individual variability of pharmacokinetic parameters, greater correlation between pharmacokinetic parameters and for trough concentration relationship, and reduced sensitivity to the effects of food on absorption.[2-4]

Clinical Experience: Several studies comparing the two oral formulations of cyclosporine in renal and liver transplant recipients conÞrm that Neoral® is as safe and well tolerated as Sandimmune® for long-term maintenance treatment. Neoral® also compared favorably to Sandimmune® with regards to graft function.

Adverse Effects: The principal adverse reactions associated with cyclosporine are renal dysfunction, tremor, hirsutism, hypertension, and gum hyperplasia. Other adverse reactions include hypomagnesemia, nausea, vomiting, and rarely seizures.

Drug Interactions: Cyclosporine is extensively metabolized in the liver by cytochrome P-450 III-A microsomal enzymes. Substances that inhibit this enzyme system can decrease cyclosporine metabolism and increase its blood concentrations. Substances that are inducers of cytochrome P-450 activity can increase cyclosporine metabolism and decrease its blood concentrations. Several drugs are known to act on this enzyme system. Drugs that increase cyclo-sporine concentrations include verapamil,

diltiazem, ketoconazole, itracona-zole, erythromycin, and clarithro-mycin. Drugs that decrease cyclosporine levels include rifampin, phenytoin, phenobarbital, and carbamazepine. Monitoring of cyclosporine concentrations and appropriate dosage adjustment are essential when these drugs are used concomitantly.

Concomitant use of nephrotoxic drugs (such as amphotericin, aminoglycosides, and vancomycin) may potentiate the renal dysfunction of cyclosporine. Careful monitoring of renal function should be practiced when these agents are used with cyclosporine.

Precautions and Contraindications: Neoral® is contraindicated in patients with hypersensitivity to cyclosporine or to any of the ingredients of the formulation.

Cyclosporine can cause nephrotoxicity and hepatoxicity when used in high doses. Cyclosporine is rated as Pregnancy Category C. In animal studies it was embryo- and feto-toxic. In case reports of pregnant women (most of whom were transplant recipients), most pregnancies had complications including: premature birth, low birth weight, pre-eclampsia, eclampsia, abrupto placentae, oligohydramnios, Rh incompatibility, and fetoplacental dysfunction. Malformations were also reported in 5 viable infants. Therefore, the risks and beneÞts of using cyclosporine during pregnancy should be carefully weighed.

Dosage and Administration: The daily dose of Neoral® should always be given in two divided doses. Neoral® should be administered on a consistent schedule with regard to the time of day and in relation to meals. To make Neoral® oral solution more palatable, it should be diluted, preferably with orange or apple juice that is at room temperature. Grapefruit juice alters the metabolism of cyclosporine and should be avoided. The combination of Neoral® oral solution and milk can be unpalatable.

Conversion from Sandimmune® to Neoral®: The Pharmacy and Therapeutics Committee recently approved a proposal to change the oral formulation of cyclosporine available at the Clinical Center from Sandimmune® to Neoral®. Sandimmune® and Neoral® are not interchangeable, and patients should be monitored closely when therapy is changed.

All Clinical Center patients for whom cyclosporine therapy is indicated should be started on the Neoral® formulation. All patients who are currently on Sandimmune® should be switched to Neoral® with their next prescription reÞll. The following guidelines should be followed for conversion:

1. Start Neoral® at the same daily dose as was previously used with Sandimmune® (1:1 dose conversion). If the patient is suspected of having malabsorption, the better absorption proÞle of Neoral®

should be taken into consideration. Neoral® should always be prescribed for twice daily (q12h) dosing.
2. Monitor cyclosporine blood trough concentrations every 4 to 7 days after conversion, and adjust the Neoral® dose until the level equals the pre-conversion value.
3. Monitor clinical safety parameters such as serum creatinine and blood pressure every two weeks during the Þrst two months after conversion.

Cost: The table below summarizes the acquisition costs of the available forms of cyclosporine. Costs are based on the federal supply schedule.

Agent	25 mg capsule	100 mg capsule	Oral solution
Sandimmune®	$22.61/box of 30	$90.97/box of 30	$151.45/50 ml
Neoral®	$24.17/box of 30	$96.38/box of 30	$160.23/50 ml

Conclusions: Neoral® is an improved oral formulation of cyclosporine. It appears to be equal to Sandimmune® in terms of safety and efÞcacy. Neoral® offers the advantage of more complete and consistent absorption which may, in some cases, allow for decreased cyclosporine doses and a decreased need for blood level monitoring. Patients who are switched from Sandimmune® to Neoral® should be closely monitored.

References

1. Neoral® package insert. Sandoz Pharmaceuticals Corporation. September 1995.
2. Noble S, Markham A. Cyclosporin: A review of the pharmacokinetic properties, clinical efÞcacy and tolerability of a microemulsion-based formulation. Drugs 1995;59:924-41.
3. Holt DW, Mueller EA, Kovarik JM et al. The pharmacokinetics of neoral: A new oral formulation of cyclosporine. Transplant Proc 1994;26:2935-9.
4. Kahan BD, Dunn J, Fitts C et al. Reduced inter- and intra-subject variability in cyclosporine pharmacokinetics in renal transplant recipients treated with a microemulsion formulation in conjunction with fasting, low-fat meals, or high-fat meals. Transplantation 1995;59:505-11.
5. Niese D, Buchholz B, Land W et al. A double-blind randomized study of Sandimmun Neoral versus Sandimmun in new renal transplant recipients: Results after 12 months. Transplant Proc 1995;27:1849-56.
6. Frei U, Taesch S, Niese D et al. Use of sandimmun neoral in renal transplant patients. Transplant Proc 1994;26:2928-31.
7. Levy G, Altaif I, Rezieg M et al. Cyclosporine neoral in liver transplant recipients. Transplant Proc 1994;26:3184-7.

Medication Utilization Evaluation: Omeprazole (Prilosec®)

Omeprazole (Prilosec®) is a substituted benzimidazole compound with potent antisecretory properties. It suppresses gastric acid secretion by inhibiting the H+/K+ ATPase enzyme system (proton pump) at the surface of the gastric parietal cell. Omeprazole has been available at the Clinical Center since 1989. Use of omeprazole at the Clinical Center has gradually increased as the number of approved indications for the drug has increased. In Þscal year 1995, omeprazole accounted for $279,177 of the Pharmacy Department's drug budget.

The Pharmacy and Therapeutics Committee in cooperation with the NIDDK Digestive Diseases Branch recently approved guidelines for the use of omeprazole. The following indications were considered appropriate justiÞcations for use of omeprazole at the Clinical Center:

- Endoscopically proven gastric ulcer refractory to treatment for 8 weeks with histamine H2-receptor antagonist
- Endoscopically proven duodenal ulcer refractory to treatment for 8 weeks with histamine H2-receptor antagonist or sucralfate
- Endoscopically proven grade 3 or 4 reþux esophagitis
- Endoscopically proven reþux esophagitis refractory to treatment for 3 months with histamine H2-receptor antagonist
- Hypersecretory conditions (e.g., multiple endocrine adenomas, systemic mastocytosis, Zollinger-Ellison Syndrome)
- Endoscopically proven Barrett's esophagus
- Helicobacter pylori eradication in conjunction with antimicrobial agents

The Pharmacy and Therapeutics Committee undertook a review of omeprazole use at the Clinical Center.

Methods: A retrospective review of medical records was conducted. A search of the hospital's Medical Information System was used to identify patients (inpatients and outpatients) who had received omeprazole between January and April of 1996. The Þrst 100 records were reviewed. Basic demographic data regarding patients and prescribers were collected. Additionally, information about the indication for omeprazole use and dosage regimen were collected. Information about medication-related adverse effects was not collected because of the limitations of retrospective reviews.

Results: Of the 100 medical records reviewed, only 75 contained sufÞcient documentation about omeprazole to be considered evaluable. In each of these cases, omeprazole was prescribed appropriately for indications consistent with the Clinical Center guidelines. The dosage regimen in all of these cases was also appropriate. Fifty-Þve of the orders were for patients

with various hypersecretory conditions (mostly Zollinger-Ellison Syndrome). Sixty-two of the omeprazole orders were prescribed by physicians from the National Institute of Diabetes and Digestive and Kidney Diseases.

Conclusions: Omeprazole prescribing, where clearly documented in the medical record, is appropriate. The dosing regimens and indications for use are consistent with accepted guidelines. The indications for omeprazole use are not always clearly documented in the medical record. Clinicians should be familiar with the Clinical Center's guidelines for omeprazole use and clearly document the indication for omeprazole (and other medications) in the medical record.

Formulary Update

The Pharmacy and Therapeutics Committee recently approved the following formulary actions:

Additions

- Albendazole (Albenza™), a broad-spectrum, oral antihelmintic agent
- Cisatracurium (Nimbex®), an intermediate acting, non-depolarizing neuromuscular blocker
- Remifentanyl (Ultiva®), a short-acting, mu-opioid receptor agonist
- Elliott's B solution, a vehicle for intrathecal drug administration
- Insulin lispro (Humalog®), an anlog of regular human insulin
- Testosterone transdermal system (Androderm®)
- Cyclosporine (Neoral®)
- Clomiphene (Clomid®), an ovulation stimulant

Deletions

- Nadolol (Corgard®)
- Propoxyphene (Darvon®)

Did You Know...

The FDA approved a record 53 new molecular entities in 1996. Of these, 47 are for therapeutic use and 6 are diagnostic agents.

Donepezil (Aricept®) has been approved for the treatment of mild to moderate Alzheimer's disease. This agent joins tacrine (Cognex®) as the only agent sapproved for the treatment of this disease.

Two new once-daily oral quinolones have recently been approved by the FDA Sparþoxacin (Zagam®) is indicated for use in the treatment of community-acquired pneumonias and bacterial exacerbations of bronchitis.

Levoþoxacin (Levaquin®) was approved for use in respiratory tract infections as well as certain skin, kidney, and urinary tract infections. It is also available in a parenteral formulation.

Somatropin [rDNA origin] (Nutropin®) recently gained approval for the treatment of growth failure associated with Turner syndrome.

Editor's Note

We wish to thank Cynthia Dunbar, M.D. for reviewing the article on cyclosporine, and acknowledge Michelle Plante, Pharm.D. and Melissa Johnson, Pharm.D. for their contributions to this issue of Pharmacy Update.

Designed by Richard Barnes, NCRR, MAPB.
